NCERQA STAR GRANT ABSTRACT

EPA Grant Number: *(please leave blank, I will add later)*
Title: Pollution-Enhanced Allergic Inflammation and Phase II Enzymes (Project 2)
Investigator(s): David Diaz-Sanchez, PhD; Adrian Casillas, MD
Institution: University of California, Los Angeles
EPA Project Officer: Chris Saint
Project Period: 4/1/04 - 3/31/05
Project Amount: $119,877
Research Category: Children's Vulnerability to Toxics

Objectives/Hypothesis:
The goal of this study is to determine the role of Phase II enzymes in regulating severity of responses to particulate pollutant-enhanced allergic inflammation in children. Oxidative stress occurs as a consequence of inflammation in allergic airway diseases such as asthma and rhinitis. Oxidant pollutants such as diesel exhaust particles (DEP) cause an additional oxidative burden in the respiratory tract and thereby mediate their biological effects. A consequence of oxidative stress is the induction of genes that contain the antioxidant response element (ARE) e.g. Phase II enzymes. These enzymes have potent antioxidant effects that potentially may counteract the oxidant effects of the pollutants. Our central hypothesis is that generation of these protective enzymes govern the extent of the pro-inflammatory and pro-allergenic effects of oxidant pollutants and are reduced in susceptible sub-populations (such as children and asthmatics).

Approach:
We will study the role of Phase II enzymes in regulating responses to pollutants in: children's upper airways (Aim #1); the lower airways of healthy and asthmatic individuals (Aim #2) and in mechanistic animal and cellular models of allergic inflammation (Aim #3). Aim #1 will test the hypothesis that Phase II enzyme expression in the upper airways are induced by oxidant pollutants and differ between children and adults. This will be accomplished by determining whether nasal challenge with DEP will induce gene expression of key Phase II enzyme in the upper airways, whether this expression in response to DEP differs between children and adults and whether enhanced cellular responses to DEP in children correlate with Phase II enzyme gene expression. Aim #2 will test the hypothesis that Phase II enzyme expression in the lower airways are induced by oxidant pollutants and differ between asthmatic and non-asthmatic subjects. This will be accomplished by exposing healthy and asthmatic individuals to diesel exhaust and comparing Phase II enzyme gene expression in sputum. Aim #3 will determine the role of Phase II enzymes in regulating the adjuvant effects of oxidant pollutants. This will be accomplished by determining whether induction of Phase II enzymes can ameliorate the effects of DEP on allergic inflammation in an in vivo mouse model and by determining whether induction of

Phase II enzymes can inhibit DEP-induced mast cell histamine and IL-4 release or cytokine production from epithelial cells.

Expected Results:

Allergic airway disease (rhinitis, asthma) is a major health problem in children. The potential benefits to society are an increased understanding of how the body's natural defenses regulate pollution-induced allergic and inflammatory responses. In addition, we will potentially gain important insights into which groups of people may have increased susceptibility to the deleterious effects of pollutants.

Supplemental Keywords: (do not duplicate terms used in text)